November 15, 2001

Dawn E. Hynes
Schenectady International Inc.
P.O. Box 1046
Schenectady, New York 12301

Dear Ms. Hynes:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Alkylphenols, posted on the ChemRTK Web Site on, May 18, 2001. I commend Schenectady International Inc. for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA has a number of comments on the submission, as explained more fully in the Comments document. Our overall conclusion is that the alkylphenols category as proposed lacks the predictive strength to conduct the extrapolations described in this submission. We recommend that you reconsider your early approach based on smaller, more closely defined categories.

The *in vitro* mammalian cell mutagenicity endpoint has not been adequately addressed and we believe additional testing is necessary. The robust summaries for bacterial mutagenicity need revision to correct deficiencies. The repeated dose and reproductive and developmental toxicity endpoints are not adequately characterized for some category chemicals that are significantly different from any of the tested materials.

Some aquatic toxicity tests are inadequate because exposure times were well short of the standard test duration. The company needs to supply information missing from the remaining robust summaries.

EPA emphasizes that the company should provide measured rather than estimated data to fill most physicochemical data gaps. For estimating transport and distribution, EPA recommends using the Fugacity Level III Model rather than the Level I Model; the company's intentions in this regard are somewhat unclear (see the Comments).

The discussion of biodegradation data is not adequate to permit an evaluation of the test plan for this endpoint; summary information like that provided for other endpoints would be helpful.

Finally, we need to point out that two of the chemicals in your submission, 2-*tert*-butylphenol (CAS No. 88-18-6) and 2,4,6-tri-*tert*-butylphenol (CAS No. 732-26-3), are listed in the notice of Proposed Rulemaking (NPRM) published on December 26, 2000 in the Federal Register (65 FR 81658). These chemicals, voluntarily sponsored by your company *after* this notice was published, are considered *viable commitments* under the HPV Challenge Program and, as such, must meet the requirements for viable commitments described on the Chemical Right-to-Know web site (www.epa.gov/chemrtk) and in the December 26, 2000 Federal Register Notice (65 FR 81686) for the HPV Initiative. For viable commitment chemicals, in addition to meeting the requirements for chemicals sponsored under the HPV Challenge Program, full copies of any unpublished or newly conducted studies must be submitted with those relevant robust summaries used to characterize the endpoints in question. However, since these chemicals are also listed under the proposed test rule, they are subject to the requirements as stated in Unit III.D.1.b of the NPRM: if a viable commitment is made and fulfilled, and the information submitted to the Agency is deemed adequate, EPA would not include that chemical in a final TSCA section 4 HPV rulemaking. Until such time, the chemicals will remain subject to the Proposed Test Rule.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that Schenectady International advise the Agency, within 90 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

**EPA Comments on Chemical RTK HPV Challenge Submission:**
**Alkylphenols Category**

**SUMMARY OF EPA COMMENTS**

The sponsor, Schenectady International Inc., submitted a Test Plan and Robust Summaries to EPA dated April 13, 2001, for the Alkylphenols Category. EPA posted the submission on the ChemRTK HPV Challenge Web site on May 18, 2001. The proposed information-gathering plan is for 17 substances (see Category Definition below) considered by the sponsor to constitute a category.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The proposed category was not adequately justified for environmental fate data and health effects and ecological effects endpoints. The category approach for aquatic toxicity may be reasonable for considering acute toxicity of the more water-soluble chemicals in the category. However, the submitter has not addressed aquatic toxicological concerns for acute and chronic toxicity of the more lipophilic chemicals in the category (see Category Justification). Furthermore, several inadequacies in robust study summaries compound the problem of evaluating the category for aquatic toxicity.

2. Physicochemical and Environmental Fate Data. EPA emphasizes that the submitter should provide measured data to fill most physicochemical data gaps where only estimates are provided. Furthermore, the discussion of biodegradation data is not adequate to permit an evaluation of the endpoint. For

estimating transport and distribution, the sponsor used the Fugacity Level I Model. EPA recommends using the Level III Model (see Test Plan comments below).

3. Health Endpoints. The test plan appears adequate for acute toxicity and bacterial mutagenicity endpoints, pending revision of robust summaries. However, the *in vitro* mammalian cell mutagenicity endpoint has not been adequately addressed and we believe additional testing is necessary. The test plan for repeated dose toxicity and reproductive and developmental toxicity does not appear to satisfy these endpoints for chemicals that are significantly different from any of the tested materials (see explanation under Test Plan). EPA believes that with the exceptions noted below, the planned data set lacks the predictive strength to conduct the extrapolations proposed in this submission and recommends that the sponsor reconsider their initial approach that used smaller categories.

4. Ecological Effects. It appears that only two of the four daphnid tests in Table 3 of the Test Plan and elsewhere can be considered adequate once information missing from the robust summaries is submitted. The remaining two 24-hour daphnid tests are inadequate because a 48-hour exposure is the standard test duration. Similarly, a submitted algal test of six hours' duration is invalid because a 96-hour exposure duration is required to evaluate algal toxicity. The submitter needs to supply information missing from the remaining robust summaries (see Specific Comments on Robust Summaries).

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

## EPA COMMENTS ON THE ALKYLPHENOLS CATEGORY CHALLENGE SUBMISSION

### General

Many of the robust summaries do not meet minimal standards. Therefore, these robust summaries need revision to be acceptable as public information products for the Challenge Program. In some cases the summarized study is inadequate due to inappropriate test methods (see Specific Comments on Robust Summaries). EPA has provided specific comments on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance found at http://www.epa.gov/chemrtk/guidocs.htm.

### Category Definition

The proposed alkylphenol category contains 17 chemicals considered by the submitter to constitute a category. All members of this category consist of phenol bearing one or more alkyl or phenylalkyl group(s) on the benzene ring.

The submitter (Test Plan, page 11, 2nd paragraph) indicates that four 4-substituted phenols–*p*-heptylphenol (PHP), *p*-octylphenol (POP), *p*-nonylphenol (PNP), and *p*-dodecylphenol (PDDP)–are made from "mixture[s] of isomeric olefins." In other words, each of these chemicals is probably a mixture of isomeric straight chain and branched alkylphenols. EPA believes that the submitter should address the compositions of these four chemicals in more detail because they could affect the interpretation of test results, for biodegradation, for example.

### Category Justification

The submitter justifies this category with a consideration of physicochemical properties, environmental distribution and fate, aquatic toxicity, and limited mammalian toxicity information. The submitter notes that, initially, the alkylphenol category was conceived as four separate categories based on the type of substituent and its position on the ring. After evaluation of the available information, however, the

submitter concluded that, “overall, the available data did not support individual categories. The initial categories were, therefore, combined.”

EPA has concerns about generalizing the test results of some individual category members to the entire group, such as assuming similar toxicities for phenols with highly branched substituents in the 2-position (having a hindered phenolic group), and those without 2-substituents. EPA believes that overall, the category proposed lacks the predictive strength to conduct the extrapolations proposed in this submission and recommends that the sponsor reconsider their initial approach that used smaller categories.

For mammalian toxicity, the submitter considered the consistency of the genotoxicity and acute oral toxicity data to support these chemicals as a category. The data suggest that this is a reasonable approach for these two endpoints, as the genotoxicity data were uniformly negative for all ten chemicals that had data and acute oral toxicity was low for the 15 chemicals that had data. The submitter also tried to establish that the repeated dose, reproductive, and developmental toxicity data were consistent and supported drawing general conclusions about alkylphenols as a class. However, adequate repeated-dose toxicity data were available for only four chemicals and reproductive/developmental toxicity data were available for only three chemicals. EPA considered these data were too limited to fully support the arguments made by the submitter.

For aquatic toxicity, the submitter fails to explain how the limited available measured and predicted chronic toxicity data enter into the category justification and test plan. EPA believes that the sponsor should consider chronic toxicity testing for the more lipophilic chemicals in the category, as the chronic testing is included in SIDS for such situations. In addition, the submitter needs to explain how the acute toxicity boundaries have been determined and how they hold together for the entire data set. For example, signs of acute toxicity have been shown for 4-nonylphenol, and the test plan does not address whether this is a concern for the more lipophilic chemicals of the series.

**Test Plan**

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)

The submitter, in its Physical Chemistry Properties table, provides a mix of measured and calculated data for these endpoints with no apparent pattern. In some cases it provides complete measured data (e.g. 4-*tert*-octylphenol (CAS 104-66-9)), and in other cases provides mostly calculated data (e.g. 4-dodecylphenol (CAS # 210555-94-5)). EPA recommends that the submitter provide measured values for melting point, boiling point, vapor pressure, and water solubility for all 17 chemicals of this category.

Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity)

*Fugacity:* The submitter states on page 4 of the Test Plan that "The level I fugacity modeling shows that, in general, phenols will be located primarily in the soil compartment. . .", and Table 2 (page 7 of 503) presents Level I Fugacity Modeling results. The Test Plan Table for environmental fate testing on page 21 also indicates that the transport/distribution values were calculated (denoted by "C", possibly using the Level I model); however, a footnote to this table shows "T = Testing required (Level III Fugacity Model to be run)". The submitter needs to provide clarification; EPA prefers the Level III Fugacity Model.

*Biodegradation:* EPA was unable to evaluate the biodegradation aspect of the test plan. On page 4 of the Test Plan the submitter states: "In general the laboratory test data showed, as expected, that the lower molecular weight phenols with simple straight-chain substituents were more biodegradable than those with higher molecular weights and more branching." However, the submission did not include a more detailed discussion of the data in the category context nor a table or other format that would facilitate analysis of the available information (such tables were provided for physicochemical properties and aquatic toxicity). EPA's preliminary impression from the test plan is that additional testing may be needed in order to adequately characterize the biodegradation of these chemicals. The submitter needs to provide an expanded discussion for this endpoint and consider whether additional testing is necessary to fully characterize the category.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

*Acute Toxicity*: Information on acute toxicity is available in the robust summaries for 15 of the 17 members of the alkylphenol group (acute oral toxicity data for 15 members, acute inhalation toxicity data for three members, and acute dermal toxicity data for four members).

The submitter concludes that the existing data on acute toxicity are adequate for 14 of the 17 group members, and that the acute toxicity endpoint requirements are satisfied by the group approach for the other three chemicals (4-*tert*-amylphenol, 4-dodecylphenol, and 2,4-bis(″,″-dimethylbenzyl)phenol). On this basis, the submitter concluded that no additional acute toxicity testing is required for any member of the group.

EPA agrees that the results of the studies show low acute oral toxicity for the tested alkylphenols and there is no reason to expect higher toxicity in the untested chemicals.

EPA agrees that existing acute oral data are adequate for five category members (p-*tert*-butylphenol, 2-*tert*-butylphenol, 4-octylphenol, 2,4-di-*tert*-butylphenol, and 4-(″,″-dimethylbenzyl)phenol). However, the robust summaries were not adequate for the remaining nine chemicals that the submitter considered to have adequate studies; see specific Comments on Robust Summaries. It is clear from the robust summaries that the studies for 2,3,6-trimethylphenol, *2-sec*-butyl phenol, 4-heptylphenol and 2,6-di-*tert*-butylphenol were inadequate; however, these studies provide general information on acute oral toxicity. For the remaining five chemicals, it is possible that the studies are adequate. If the summaries are improved and the validity of these studies is supported, additional oral testing may not be needed.

*Repeated Dose Toxicity:*

The submitter provided robust summaries for repeated-dose toxicity studies on five of the 17 chemicals: 4-*tert*-butylphenol, 4-*tert*-octylphenol, 2,6-di-*tert*-butylphenol, 4-nonylphenol, and 2,4,6-tri-*tert*-butylphenol. The submitter considered the data to be adequate for all five of these chemicals. Even though repeated-dose data are absent for the remaining 12 substances, the submitter concluded that these data gaps were filled by using the category approach, and no additional repeated-dose toxicity studies were necessary.

EPA does not agree that data are adequate for all five of the chemicals tested. Both studies for 4-*tert*-butylphenol were inadequate because of the use of a single dose level. Although the repeated-dose studies for the other four chemicals appear to be adequate, their robust summaries lack some critical information (comments below), and therefore the submitter needs to provide this information to satisfy this endpoint. EPA believes that these data are too limited and structural variation too great to characterize chemicals that are significantly different or to allow generalization to the category as a whole.

*Genetic Toxicity Data:*

The submitter's test plan notes adequate bacterial mutagenicity studies for ten chemicals and use of the category approach to satisfy the testing requirement for the remaining seven chemicals. EPA agrees that this is a reasonable approach because most of the category members have been adequately tested and all of the existing bacterial mutagenicity studies are negative. However, robust summaries for all of the chemicals other than 4-heptylphenol are lacking experimental details needed to fully evaluate the studies and should be improved.

With regard to *in vitro* assays for genotoxicity in mammalian cells, the test plan states a need for additional testing of 4-*tert*-butylphenol in light of an inadequate mouse lymphoma mutation assay with this chemical that produced ambiguous results. The test plan indicates that existing tests for 2,6-di-*tert*-butylphenol and 4-nonylphenol are adequate and that the testing requirement for the remaining chemicals is satisfied by the category approach. The robust summaries for these studies need to provide additional critical information. Although the data for three chemicals are consistently negative, testing on additional chemicals is warranted to provide more confidence in extrapolating these results to the alkylphenols as a group.

The test plan indicates the presence of adequate *in vivo* mammalian genotoxicity assays for both 2,6-di-*tert*-butylphenol and 4-nonylphenol, although the test in the former was not actually an *in vivo* study, but rather an assay for DNA repair carried out *in vitro* using primary rat hepatocytes. The study of 4-nonylphenol appeared to be an adequate micronucleus assay, although the robust summary contained only minimal information about the study. EPA believes that additional information needs to be provided in the robust summary for the 4-nonylphenol micronucleus study.

*Reproductive and Developmental Toxicity*:

The test plan indicates that there are adequate reproductive/developmental studies for 4-*tert*-octylphenol, 2,6-di-*tert*-butylphenol, and 4-nonylphenol. The testing requirement for the remaining chemicals is said to be satisfied by the category analogy to the three chemicals with data. EPA agrees that the studies for the three chemicals with data appear to be adequate, and the robust summaries are adequate as well (with the exception of the developmental toxicity summary for 2,6-di-*tert*-butylphenol). However, EPA believes that these data are too limited and structural variation too great to characterize the remaining substances or allow generalization to the category as a whole.

Ecotoxicity

Several summaries were either deficient or inadequate (see Specific Comments on Robust Summaries). For those summaries that are deficient the submitter needs to provide missing data in order for reviewers to evaluate the adequacy of the test plan.

The submitter states that no further testing is necessary to characterize the aquatic hazard of the alkylphenols category. However, EPA believes that testing is needed for chemicals where the data have been considered inadequate. In addition, the submitter needs to determine and explain the limits where acute or chronic toxicity is not likely to occur.

*Specific ecotoxicity testing recommendations*

EPA recommends that at least one or more of the least water-soluble chemicals (2,4-di-*tert*-pentylphenol, 4-dodecylphenol, 4-*sec*-butyl-2,6-di-*tert*-butylphenol, 2,4,6-tri-*tert*-butylphenol, 2,4-bis(alpha, alpha-dimethylbenzyl)phenol) need to be tested (see the bottom of Table 3, Summary of Acute Aquatic Toxicity Data for Alkylphenols, in the sponsor's Test Plan). Prior to testing, water solubility should be measured for each of these chemicals to determine which chemicals are the best candidates to show effects within the overall aqueous solubility range. The ecotoxicity tests should be done using OECD guidelines #203 (fish), #202 (daphia), and #201 (algae). EPA suggests using a closed system and mean measured concentrations during these tests. In addition, the sponsor should consider chronic testing using daphnia. The submitter has used SAR for predicting toxicity; however, EPA believes that SAR is not a good predictor for higher log P chemicals of this type.

## SPECIFIC COMMENTS ON ROBUST SUMMARIES

### Environmental Fate

*Biodegradation*

In the BIOWIN calculations, the submitter provides results in days, weeks, or months. EPA recommends that the submitter at least provide a conclusion on the degree of biodegradability of the chemical (readily, biodegrades slowly, does not biodegrade, etc.)

### Health Effects

*Acute Toxicity*

*2,4-Di-tert-butylphenol:* The number of animals per sex per dose was reported to be 30 males and 30 females; however, the results suggest group size of 5 males and 5 females. Gross necropsy results are not included.

*4-", "-Dimethylbenzylphenol*: Clinical signs and the method used to derive $LD_{50}$ are not mentioned in the study summary.

*2,3,6-Trimethylphenol*: No information is provided on the number of animals used, number that died, clinical signs, necropsy data.

*2-sec-Butylphenol*: It appears that more than one study is summarized, but the results are presented in a confusing manner. In addition, the results indicate the $LD_{50}$ value to be greater than 200 mg/kg and less than 2000 mg/kg while the next sentence states that there were no deaths.

*4-Heptylphenol:* There are insufficient doses to estimate $LD_{50}$ value or threshold for acute toxicity.

*4-tert-Octylphenol:* No information is provided on number of animals used in the study.

*4-Nonylphenol*: No information is provided on the number of animals used in the study, doses, dose-response or acute toxicity.

*2,4-Di-tert-pentylphenol:* No information is provided on the number of doses, or dose levels or threshold for acute toxicity.

*4-sec-Butyl-2,6-di-tert-butylphenol*: No information is provided on the number of doses, or dose levels or threshold for acute toxicity.

*2,4,6-Tri-tert-butylphenol*: No information is provided on dose levels administered.

*Repeated Dose Toxicity*

*2,6-Di-tert-butylphenol*: Information on the magnitude of changes noted at 100 and 600 mg/kg/day and/or their statistical significance (serum metabolites, organ weights, and histopathology) needs to be included in the study summary to facilitate evaluation of the study.

*4-Nonylphenol*: Information on the magnitude of changes noted (at 400 mg/kg/day in the 28-day study and at 150 mg/kg/day in the 90-day study) and/or their statistical significance needs to be included in the study summary to facilitate evaluation of the study.

*2,4,6-Tri-tert-butylphenol:* The robust summary for the 24-month dietary feeding study in rats does not provide information on food intake levels or on ingested doses, nor is the description always clear on which effects are statistically significant. The robust summary should be strengthened to address these limitations.

The 11-day feeding study in dogs is considered inadequate because of the short exposure duration. The robust summary failed to report the magnitude, frequency, and statistical significance of some of the reported adverse effects.

*4-tert-Butylphenol:* In the 20-week dietary feeding study in hamsters, only a single dose was tested. Effects were noted on body weight, liver weight, and the epithelium of the forestomach.

In the 51-week feeding study, rats were exposed to one level (15,000 ppm) only. Effects were noted on body weight, organ weight, and in the forestomach. In addition, information on dietary intake or the presence or absence of clinical signs or hematological or biochemical changes was not provided in the robust summary.

Neither of these two studies is considered to be adequate to characterize repeated dose toxicity because both were single dose studies that provide no dose-response information, effects were noted at the dose level tested, and therefore one cannot identify a NOAEL.

*Genetic Toxicity Data*

Genetic toxicity–Bacterial

The use of the positive controls and occurrence of cytotoxicity were not mentioned in the study summaries.

Genetic toxicity–Mammalian (in vitro)

The robust summaries need to provide additional information on method details and results.

*4-tert-Butylphenol:* The study produced ambiguous results (no evidence of mutagenicity after 3 hours, but positive results after 24 hours), and the robust summary provided insufficient details regarding study methods and results (e.g., no information concerning controls) to evaluate these findings.

Genetic toxicity–Mammalian (in vivo)

*4-Nonylphenol:* Although the mouse micronucleus study appeared to be adequate, the robust summary contains minimal details of methods and results.

Reproductive Toxicity Data

*4-tert-Octylphenol*: Dose equivalence (mg/kg/day) for the dietary concentrations of 4-*tert*-octylphenol needs to be provided in the robust summary.

Reproductive/Developmental Toxicity Data

*2,6-Di-tert-butylphenol:* The results of a single Reproductive/Developmental Toxicity Screening test (OECD guideline 421) are presented in two separate robust summaries (one for toxicity to reproduction and one for developmental toxicity). The submitter has revised values for NOAEL and LOAEL for both reproductive and developmental toxicity because an error had occurred during transcription of the original report into the SIDS document. The revised values have been incorporated and discussed in the robust summary for only reproductive toxicity. The robust summary for developmental toxicity does not address the revised values.

**Environmental Effects and Ecotoxicity Studies**

*2,3,6-Trimethylphenol:*

Fish. The 96-h $LC_{50}$ value is a range-finding value of 10-22 mg/L, and not a true $LC_{50}$ value. However, in this case because the range is narrow and is in good agreement with a well-supported SAR-predicted value, these data are considered valid pending receipt of missing robust summary data elements. Some of the missing data elements from the robust summary are pH, water hardness, DO, measured/nominal concentrations, temperature, and percent purity.

Daphnia. The data for this test are considered inadequate because a short exposure duration of 24-hour was used instead of the accepted 48-hour exposure.

Algae. The algal study summary lacks method details and information on percent purity, water hardness, pH, measured/nominal concentrations, and temperature.

*4-tert-Butylphenol*

Daphnia. The percent chemical purity of the test substance and DO content need to be provided before an assessment for data adequacy can be made.

Algae. EPA considered this study invalid because a short exposure duration of six hours was employed instead of 96 hours.

*Heptyl derivs (4-heptylphenol*)

Fish. The percent chemical purity of the test substance needs to be provided before an assessment for data adequacy can be made.

Algae. The percent chemical purity of the test substance, pH, and water hardness need to be provided before an assessment for data adequacy can be made.

*4-tert-Octylphenol*

Algae. The percent chemical purity of the test substance, pH, and water hardness need to be provided before an assessment for data adequacy can be made.

*2,6-Di-tert-butylphenol*

Fish. The 96-hour fish toxicity study summary lacks method details and information on pH, percent chemical purity, water hardness, DO, TOC, and temperature. In the 14-day fish test, pH and water hardness were missing data elements that need to be submitted before data adequacy can be determined.

Algae. In the summary of the 96-hour algal test performed in 1988 using *Selenastrum capricornutum*, the information on water hardness needs to be provided before an assessment for data adequacy can be made.

Daphnia. Both daphnia 24-hour tests are considered inadequate because a 24-hour exposure period was used instead of the accepted 48-hour exposure in the daphnid toxicity test.

*4-Nonylphenol*

Fish. The following information for the fish acute and chronic tests robust summaries needs to be provided before an assessment for data adequacy can be made: pH, water hardness, number of tests, replicates of each tests, DO content, and water temperature.

Algae. The algal test robust summary lacks method details and information on water condition (pH, temperature, and water hardness).

Daphnia. The daphnia acute and chronic studies summaries lack method details and information on pH, DO content, water hardness, water temperature, quantity of solvent used, percent purity of the test substance, measured/nominal concentration, and TOC. The 21-day reproduction study summary also lacks method details and information on pH, water hardness, DO content, percent purity of the test substance, and TOC.

**Followup Activity**

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.